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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

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OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

MEMORANDUM

Date: 8/9/05

SUBJECT: **Myclobutanil** Human Health Risk Assessment for the Proposed Section 18 Use on Soybeans (ID No: 04MN006), Legume Vegetables (except Soybeans), and Foliage of Legume Vegetables (except Soybeans) (ID No: 05FL08 & 05TN08).

DP Barcode:	D317318 & D317319, D318347	Decision No.:	357007 & 357008, 335707
Chemical#:	128857	Class:	Fungicide
Trade Name:	Laredo EC Laredo EW	EPA Reg#:	62719-412 62719-493
40 CFR:	§180.443	Chem Class:	triazole

Regulatory Action: Section 18 Registration Action
Risk Assessment Type: Single Chemical Aggregate

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1.0 EXECUTIVE SUMMARY

General Background

The Alternative Risk Integration and Assessment Team (ARIA) has previously recommended for the establishment of time-limited tolerances of 0.03 ppm in soybeans support of Section 18 requests for the use of myclobutanil on soybeans (04MN006, DP Barcode: D296308, J. Tomerlin, 3/22/04). The registrant has now supplied information that the existing time-limited tolerances for soybean commodities are inadequate as a result of preliminary data from on-going domestic field trials. The summary of the preliminary data indicates that a tolerance of 0.05 ppm for the residues of myclobutanil on soybeans would be appropriate rather than the existing 0.03 ppm. In addition, a time-limited tolerance of 1.0 ppm is appropriate for residues of myclobutanil in/on vegetable, legume (except soybean), Crop Group 6 and vegetable, foliage of legume (except soybeans), Crop Group 7 in support of the Section 18 request.

Assessments of human exposures and risks were conducted for acute and chronic dietary risk, exposure and risk to myclobutanil residues in water, residential exposure and risk, aggregate risk, and exposure and risk to workers.

Hazard Assessment

The database for myclobutanil is adequate for hazard characterization. Myclobutanil has low acute toxicity with the exception for ocular irritation. It is toxicity category III for oral and dermal acute toxicity, category IV for inhalation acute toxicity and dermal irritation. It is category I for ocular irritation and the myclobutanil technical is a dermal sensitizer.

In rat subchronic and chronic toxicity studies, the primary target organs are liver and testis. Liver effects include hypertrophy, hepatocellular necrosis and increased liver weight. Testicular effects include decreased weight, atrophy, hepatocellular vacuolization, bilateral aspermatogenesis, increased incidence of hypospermia and cellular debris in the epididymides, and increased incidence of arteritis/periarteritis in the testes. The mouse subchronic and chronic toxicity studies have a similar toxicity profile with the exception of testicular effects. In addition, there were increased Kupffer cell pigmentation, periportal punctate vacuolation, and individual cell necrosis of the liver. There is no evidence of carcinogenic potential in either the rat or mouse. In the subchronic dog, there are hepatocellular hypertrophy, increased relative and absolute liver weight and increased alkaline phosphatase. In the chronic dog study liver toxicity is similar with the addition of "ballooned" hepatocytes and increased in SGPT and GGT. Signs of toxicity observed in the rat 28-day dermal studies are limited to dermal irritation. There is no evidence of systemic toxicity in either dermal study.

There is no evidence of increased susceptibility in either of the developmental studies or the reproduction study. In the rat developmental study, maternal toxicity, which included rough hair coat and salivation, occurs at the same dose level as increases in incidences of 14th rudimentary and 7th cervical ribs in the fetuses. At the next higher dose there is also alopecia, desquamation and red exudate around the mouth in the dams. In the rabbit developmental study there is reduced body weight and body weight gain during the dosing period, clinical signs of toxicity and possibly abortions in the does at the same dose level that there are increased resorptions,

decreased litter size. The maternal toxicity in the rat reproduction study includes increased liver weights and hepatocellular hypertrophy. Reproductive effects also occur and include increased incidences in the number of still born pups and atrophy of the testes, epididymides and prostate. Developmental effects occurring at the same dose in the reproduction study include decreased pup body weight gain during lactation.

There is no concern for mutagenic activity. Myclobutanil has been classified as an “E carcinogen.”

Dose Response Assessment and Food Quality Protection Act (FQPA) Decision

Acute dietary endpoints: The acute dietary endpoint for females in the 13 to 50 year age group is based the no observable adverse effect level (NOAEL) for a developmental toxicity in rabbits which manifested as increases in resorptions, decreases in litter size. This endpoint is considered appropriate for females of childbearing age (13-50 years old) since the effects could occur due to a single *in utero* exposure.

There were no appropriate toxicological effects attributable to a single exposure (dose) observed in oral toxicity studies including the maternal effects in the developmental toxicity studies in rats and rabbits. Therefore, an acute dose and an endpoint were not selected for the general population for this risk assessment.

Chronic dietary endpoint: The chronic dietary endpoint is based on increased incidence of testicular atrophy in a chronic toxicity/carcinogenicity study in rats.

Short-Term (1-7 days) Oral Exposure: The short-term oral exposure endpoint is based on atrophy of the testes and prostate as well as an increase in the number of stillborn pups and a decrease in pup weight gain during lactation in a two-generation reproduction study in rat.

Intermediate-Term (7 days to several mo.) Oral Exposure: The intermediate-term oral exposure endpoint is based on atrophy of the testes and prostate as well as an increase in the number of stillborn pups and a decrease in pup weight gain during lactation in a two-generation reproduction study in rat.

Dermal Absorption: A dermal absorption factor of 50% should be used for risk assessment based on a dermal absorption study. Although this study is considered unacceptable, the study provides information indicating that absorption would be no greater than 50%. The dermal absorption factor is required for intermediate and long-term dermal risk assessment since oral doses were selected for these exposure periods. Dermal absorption is not required for short-term dermal exposure risk assessment since a dermal dose from a 21-day dermal toxicity study was selected for this time period.

Short-Term (1-7 days) Dermal Exposure: The short-term dermal exposure endpoint is based on microscopic changes, indicating irritation were observed in the skin, including epidermal necrosis, epidermal thickening, and/or subacute/chronic inflammation of the dermis in a 28-day dermal toxicity in rat. No systemic toxicity was observed at the highest dose.

Intermediate-Term (7 days to several mo.) Dermal Exposure: The intermediate-term dermal exposure endpoint is based on atrophy of the testes and prostate as well as an increase in the number of stillborn pups and a decrease in pup weight gain during lactation in a two-generation reproduction study in rat. Since an oral dose is selected, the dermal absorption factor of 50% should be applied.

Long-Term (Several Months to Life-Time) Dermal Exposure: The long-term dermal endpoint is based on increased incidence of testicular atrophy in a chronic toxicity/carcinogenicity study in rats at the NOAEL. Since an oral dose is selected, the dermal absorption factor of 50% should be applied.

Short-(1-7 days) and Intermediate-Term (7 days to several mo.) Inhalation Exposure: The short- and long-term inhalation endpoint is based on increased incidence of testicular atrophy in a chronic toxicity/carcinogenicity study in rats at the NOAEL. The inhalation exposure component (i.e., mg/L) using a 100% absorption rate (default value) should be converted to an oral equivalent dose (mg/kg/day). This oral equivalent dose should then be compared to the oral NOAEL for Short- and Intermediate-Term exposure to calculate the Margins of Exposure (MOE).

Long-Term (Several Months to Life-Time) Inhalation Exposure: The long-term dermal endpoint is based on increased incidence of testicular atrophy in a chronic toxicity/carcinogenicity study in rats at the NOAEL. The inhalation exposure component (i.e., mg/L) using a 100% absorption rate (default value) should be converted to an oral equivalent dose (mg/kg/day). This oral equivalent dose should then be compared to the oral NOAEL for Long-Term exposures to calculate the MOEs.

FQPA Determination: The FQPA Safety Factor Committee recommended that the FQPA safety factor for protection of infants and children (as required by FQPA) be **removed (1x)**. The Committee concluded that the safety factor could be removed for myclobutanil because: i. The toxicology database is complete for FQPA assessment; ii. The toxicity data provide no indication of increased susceptibility of young rats or rabbits to myclobutanil; iii. The HED Hazard Identification Assessment Review Committee (HIARC) determined that a developmental neurotoxicity study is not required; and iv. The exposure assessments will not underestimate the potential dietary (food and drinking water) and residential (non-occupational) exposures for infants and children from the use of myclobutanil.

<u>Exposure Scenario</u>	<u>NOAEL</u>	<u>Dose or Target MOE*</u>	<u>Study/Effect</u>
Acute Dietary (Females 13-50)	NOEL = 60 mg/kg/day UF = 100 Acute RfD = 0.6 mg/kg/day	FQPA SF = 1X aPAD = acute RfD = 0.6 mg/kg/day	Developmental Toxicity Study - Rats. LOAEL = 200 mg/kg/day based on increased resorptions, decreased litter size.
Acute Dietary (General Population)	None	N/A	N/A
Chronic Dietary (All populations)	NOAEL = 2.49 mg/kg/day UF = 100 Chronic RfD = 0.025 mg/kg/day	FQPA SF = 1X cPAD = chronic RfD = 0.025 mg/kg/day	Chronic Toxicity/Oncogenicity Study - Rats LOAEL = 10 mg/kg/day based on decreased testicular weights and increased testicular atrophy.
Short-Term (1-30 days) Oral	Oral NOAEL = 10 mg ai/kg/day	Residential MOE = 100 Occupational MOE = 100	2-Generation Reproduction Toxicity - Rat. LOAEL = 50 mg/kg bw/day based on atrophy of the testes and prostate as well as an increase in the number of stillborn pups and a decrease in pup weight gain during lactation.
Intermediate-Term (1-6 months) Oral	Oral NOAEL = 10 mg ai/kg/day	Residential MOE = 100 Occupational MOE = 100	2-Generation Reproduction Toxicity - Rat. LOAEL = 50 mg/kg bw/day based on atrophy of the testes and prostate as well as an increase in the number of stillborn pups and a decrease in pup weight gain during lactation.
Short-Term (1-30 days) Dermal	NOAEL = 100 mg ai/kg/day	Residential MOE = 100 Occupational MOE = 100	28-day Dermal Toxicity - Rats. There were no signs of toxicity at the high dose of 100 mg/kg a.i.
Intermediate-Term (1-6 months) Dermal	Oral NOAEL = 10 mg ai/kg/day	Residential MOE = 100 Occupational MOE = 100	2-Generation Reproduction Toxicity - Rat. LOAEL = 50 mg/kg bw/day based on atrophy of the testes and prostate as well as an increase in the number of stillborn pups and a decrease in pup weight gain during lactation.
Long-Term Dermal (> 6 months)	Oral NOAEL = 2.49 mg/kg/day	Residential MOE = 100 Occupational MOE = 100	Chronic Toxicity/Carcinogenicity - Rat LOAEL = 10 mg/kg/day based on decreased testicular weights and increased testicular atrophy.
Short-Term (1-30 Days) Inhalation	Oral NOAEL = 10 mg/kg/day	Residential MOE = 100 Occupational MOE = 100	2-Generation Reproduction Toxicity Study - Rats. LOAEL = 50 mg/kg bw/day based on atrophy of the testes and prostate as well as an increase in the number of stillborn pups and a decrease in pup weight gain during lactation.
Intermediate-Term (1-6 months) Inhalation	Oral NOAEL = 10 mg/kg/day	Residential MOE = 100 Occupational MOE = 100	2-Generation Reproduction Toxicity Study - Rats. LOAEL = 50 mg/kg bw/day based on atrophy of the testes and prostate as well as an increase in the number of stillborn pups and a decrease in pup weight gain during lactation.

Long-Term Inhalation (> 6 months)	Oral NOAEL = 2.49 mg/kg/day	Residential MOE = 100 Occupational MOE = 100	Chronic Toxicity/Carcinogenicity - Rat LOAEL = 10 mg/kg/day based on decreased testicular weights and increased testicular atrophy.
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Dietary Exposure Estimates

Residue Chemistry Tolerances are established for combined residues of the fungicide myclobutanil [alpha-butyl-alpha-(4-chlorophenyl)-1*H*-1,2,4-triazole-1-propanenitrile] and its alcohol metabolite [alpha-(3-hydroxybutyl)-alpha-(4-chlorophenyl)-1*H*-1,2,4-triazole-1-propanenitrile] (free and bound) [40 CFR §180.443(a)], ranging from 0.02 ppm on cotton seed and eggs to 25 ppm on grape raisin waste. Time-limited tolerances [40 CFR §180.443(b)] and tolerances for inadvertent residues [40 CFR §180.443(d)] have also been established.

Proposed application parameters for soybeans in the Section 18 request call for up to 2 applications of myclobutanil at an application rate of 2.0 oz (0.125 lb) a.i./A, equivalent to approximately 56 g a.i./A. The Section 18 requested a PHI of 28 days. The Section 18 for legume vegetables proposed up to 2 applications for a total of 0.50 lb a.i./A/season with 5-11 day retreatment intervals and 0-day PHI

Drinking Water Exposure Estimates

There are no health advisory levels or Maximum Contaminant Levels established for residues of myclobutanil in drinking water. The Agency used the Screening Concentration in Ground Water (SCI-GROW) to calculate myclobutanil estimated environmental concentrations (EECs) in ground water and the First Index Reservoir Screening Tool (FIRST) to calculate EECs in surface water. Model assumptions followed the use patterns for hops, which are much higher than the proposed patterns in the Section 18s. Based on the FIRST model, the EECs of myclobutanil for acute exposures are 333 ppb and 86 ppb for chronic exposures. The EEC for both acute and chronic exposures is estimated as 3.2 ppb for surface water using the SCI-GROW model. The highest estimates for acute exposure, 333 ppb, and chronic exposure, 86 ppb, were used in the dietary exposure analyses.

Dietary Exposure Analysis

HED is concerned when dietary risk exceeds 100% of the population-adjusted dose (PAD). The DEEM-FCID™ analyses estimate the dietary exposure of the U.S. population and various population subgroups. The exposure results are for the general U.S. Population, all infants (<1 year old), children 1-2, children 3-5, children 6-12, youth 13-19, females 13-49, adults 20-49, and adults 50+ years. The acute analysis is a conservative Tier 1 assessment based on tolerance-level residues and the assumption of 100% crop treated for established and proposed myclobutanil tolerances. The highest estimate for acute water concentration, 333 ppb, was used in the analysis. As this is a Tier 1 assessment, dietary exposure and risk at the 95th percentile of exposure are reported. For females 13-49 yrs old, the only population subgroup for which there is a myclobutanil acute endpoint, the exposure and risk estimates are below HED's level of concern (i.e., the percentages of the acute population-adjusted doses (aPADs) are below 100%). The exposure estimate for females 13-49 yrs old is 4% aPAD.

The chronic analysis is based on partially refined Tier 3 assumptions in that it incorporates estimates of average percent crop treated (%CT) for some crops, as well as monitoring data from apple juice, bananas (not plantains) and milk. The highest estimate for chronic water exposure, 86 ppb, was used in the analysis. The general U.S. population and all population subgroups have exposure and risk estimates which are below HED's level of concern (i.e., the percentages of the chronic population-adjusted doses (cPADs) are all below 100%). The exposure estimate for the U.S. population is 20% cPAD and for the most highly exposed subgroup, all infants <1 yrs old, is 41% cPAD.

Residential Exposure Estimates

Myclobutanil is present in numerous end-use products, including those registered for use on turf, roses, flowers, shrubs and trees. Soluble concentrate may be applied with hose-end or trigger bottle sprayers. Small-scale lawn application has the greatest potential for homeowner exposures. Short- and intermediate-term exposures are expected for residential handlers. The HIARC has determined that a 50% dermal absorption factor should be applied for intermediate-term assessments. A dermal absorption factor is not required for short-term assessments because the NOAEL used is based upon a 28-day dermal study. The estimated MOE's are based upon conservative assumptions and are >100; therefore, the estimated risks from residential non-dietary post-application exposures do not exceed HED's level of concern for myclobutanil.

Aggregate Exposure Scenarios and Risk Conclusions

Acute Aggregate Risk (Food + Water) The aggregate acute dietary risk estimates include exposure to residues of myclobutanil in food and water, and does not include dermal, inhalation or incidental oral exposure. Since the dietary exposure assessment already includes the highest acute exposure from the drinking water modeling data, no further calculations are necessary. The population subgroup of interest, females 13-49 yrs old, has exposure and risk estimates which are below HED's level of concern (i.e., the percentages of the aPAD are below 100%). The food and water exposure estimates for females 13-49 yrs old is 4 % aPAD. Therefore, the acute aggregate risk estimates associated with the proposed use of myclobutanil do not exceed HED's level of concern.

Short- and Intermediate- Term Aggregate Risk (Residential + Food + Water) For short-term aggregate exposure risk assessment, even though there was no systemic toxicity in a dermal study, by combining dermal with oral and inhalation exposures would provide the most conservative risk assessment approach. The aggregate short-term risk estimates are below HED's level of concern (MOEs < 100).

For myclobutanil intermediate-term aggregate exposure risk assessment, oral, dermal and inhalation exposures can be combined since dermal and inhalation exposures are corrected to oral-equivalent doses. The aggregate intermediate-term exposure estimates for myclobutanil do not include inhalation exposure, as there is no associated scenario. The aggregate intermediate-term exposure estimates are below HED's level of concern (MOEs < 100).

Chronic Aggregate Risk (Food + Water) For myclobutanil, chronic aggregate exposure risk assessment, oral, dermal and inhalation exposures can be combined since dermal and inhalation exposures are corrected to oral equivalent doses. However, there are no chronic residential dermal or inhalation scenarios, therefore the assessment included food and water only. Since the dietary exposure assessment already includes the highest chronic exposure from the drinking water modeling data, no further calculations are necessary. The general U.S. population and all population subgroups have exposure and risk estimates which are below HED's level of concern (i.e., the percentages of the cPADs are all below 100%). The exposure to the U.S. population was 21% cPAD and the most highly exposed subgroup, children 1-2 yrs old, at 45% cPAD. Therefore, the aggregate chronic risk associated with the proposed use of myclobutanil does not exceed the Agency's level of concern for the general U.S. population or any population subgroup.

Cancer

The HIARC classified myclobutanil as a "Group E - not likely human carcinogen" and, therefore, quantification of human cancer risk is not required.

Occupational Exposure Estimates

Based on the proposed use patterns in soybeans and legumes, occupational handlers are expected to have dermal and inhalation exposures. The lowest estimated dermal and inhalation MOEs are 1000 and 2000, respectively, for mixer/loaders. Note that the dermal MOE of 2000 is achieved only by wearing a single layer of protective clothing and gloves. Without gloves, MOEs are lower than 100. Therefore, since The Agency's level of concern for myclobutanil is for MOEs less than 100, potential risk to handlers is well below the level of concern. Therefore, the use directions for this Section must require that mixer/loaders wear gloves when handling myclobutanil.

Because of the high interest in soybean rust and the need to scout fields to confirm its presence, the Agency conducted an assessment of post-application exposures for scouting activities. The Post-application MOEs is 1000. Since the Agency's level of concern for myclobutanil is for MOEs less than 100, potential risk for occupational post-application exposures is below the Agency's level of concern.

Recommendations:

Regulatory Recommendations and Deficiencies

TRB/HED concludes that there is a reasonable certainty that no harm will result to the U.S. Population, including infants and children, from acute, short- and intermediate- term, and chronic aggregate exposure to myclobutanil residues. TRB/HED has no objection to establishing the time-limited tolerances for the residues of myclobutanil, in or on the following:

Soybeans 0.05 ppm
 Vegetable, legume (except soybean), Crop Group 6 1.0 ppm
 Vegetable, foliage of legume (except soybean), Crop Group 7 1.0 ppm

2.0 PHYSICAL/CHEMICAL PROPERTIES CHARACTERIZATION

TABLE 1. TEST COMPOUND NOMENCLATURE	
Chemical Structure	
Empirical Formula	C ₁₅ H ₁₇ ClN ₄
Common name	Myclobutanil
Company experimental name	sythane
IUPAC name	(RS)-2-(4-chlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)hexanenitrile
CAS name	-butyl--(4-chlorophenyl)-1H-1,2,4-triazole-1-propanenitrile
CAS Registry Number	88671-89-0
End-use product/EP	Laredo EC & Laredo EW (EPA Reg. No. 62719-412 & 62719-493)
Chemical Class	triazole
Known Impurities of Concern	NA

TABLE 2. PHYSICOCHEMICAL PROPERTIES		
PARAMETER	VALUE	REFERENCE
Molecular Weight	288.78	Myclobutanil Decision Document, Agriculture Canada, E93-01
Melting point/range	70-71.5 C	
Boiling point	202-208	
pH	8 to 9	
Density	1.22	
Water solubility (25 C)	142 ppm	
Solvent solubility (20 C)	Hexanes < 1g/100g Most Organics >50g/100g	
Vapor pressure (25 C)	1.6 x 10 ⁻⁶ torr	
Dissociation constant, pKa	NA	
Octanol/water partition coefficient, logP _{ow} (25 C)	2.94	
UV/visible absorption spectrum	NA	

TABLE 2. PHYSICOCHEMICAL PROPERTIES		
PARAMETER	VALUE	REFERENCE
Henry's law constant	NA	

3.0 HAZARD CHARACTERIZATION

3.1 Hazard Profile

TABLE 3. ACUTE TOXICITY PROFILE - MYCLOBUTANIL				
Guideline No.	Study Type	MRID #	Results	Toxicity Category
81-1	Acute Oral	00141662	LD ₅₀ = 1.6 g/kg (M) LD ₅₀ = 2.29 g/kg (F)	III
81-2	Acute Dermal	00141663	LD ₅₀ > 5000 mg/kg	IV
81-3	Acute Inhalation	40357101	LC ₅₀ > 5.1 m/L	IV
81-4	Primary Eye Irritation	00141663	Severe eye irritant	I
81-5	Primary Skin Irritation	00141663	Non-irritating to skin	IV
81-6	Dermal Sensitization	40357102	Positive sensitizer	

Myclobutanil has low acute toxicity with the exception for ocular irritation. It is toxicity category III for oral and dermal acute toxicity, category IV for inhalation acute toxicity and dermal irritation. It is category I for ocular irritation and the myclobutanil technical is a dermal sensitizer.

In rat subchronic and chronic toxicity studies, the primary target organs are liver and testis. Liver effects include hypertrophy, hepatocellular necrosis and increased liver weight. There is decreased testicular weight and testicular atrophy. Chronic exposure to the rat also results in hepatocellular vacuolization and additional testicular effects which include bilateral aspermatogenesis, increased incidence of hypospermia and cellular debris in the epididymides and increased incidence of arteritis/periarteritis in the testes. With the exception of testicular effects, subchronic and chronic exposure in the mouse have a similar toxicity profile. The mouse has, in addition, increased Kupffer cell pigmentation, periportal punctate vacuolation, and individual cell necrosis of the liver. There is no evidence of carcinogenic potential in either the rat or mouse. In the subchronic dog, there are hepatocellular hypertrophy, increased relative and absolute liver weight and increased alkaline phosphatase. In the chronic dog study liver toxicity is similar with the addition of "ballooned" hepatocytes and increased in SGPT and GGT. Signs of toxicity observed in the rat 28-day dermal studies (studies on the 40WP and 2EC formulations) are limited to dermal irritation. There is no evidence of systemic toxicity in either study.

There is no evidence of increased susceptibility in either of the developmental studies or the reproduction study. In the rat developmental study, maternal toxicity, which included rough hair coat and salivation, occurs at the same dose level (312.6 mg/kg/day) as increases in incidences of 14th rudimentary and 7th cervical ribs in the fetuses. At the next higher dose there is also alopecia, desquamation and red exudate around the mouth in the dams. The NOAEL is 93.8 mg/kg/day. In the rabbit developmental study there is reduced body weight and body weight gain during the dosing period, clinical signs of toxicity and possibly abortions in the does at the same dose level (200 mg/kg/day) that there are increased resorptions, decreased litter size. The NOAEL is 60 mg/kg/day. The maternal toxicity in the rat reproduction study includes increased liver weights and hepatocellular hypertrophy (LOAEL is 50 mg/kg/day; NOAEL is 10 mg/kg/day). Reproductive effects also occur at 50 mg/kg/day and include increased incidences in the number of still born pups and atrophy of the testes, epididymides and prostate. Developmental effects occurring at the same dose in the reproduction study, include decreased pup body weight gain during lactation.

There is no concern for mutagenic activity. Myclobutanil has been classified as an "E carcinogen."

3.2 FQPA Considerations

The FQPA Safety Factor Committee met on August 16, 1999 to reassess FQPA requirements (HED DOC. NO. 013734, 9/13/99). The Committee recommended that the FQPA safety factor for protection of infants and children (as required by FQPA) be **removed (1x)**. The Committee concluded that the safety factor could be removed for myclobutanil because: i. The toxicology database is complete for FQPA assessment; ii. The toxicity data provide no indication of increased susceptibility of young rats or rabbits to myclobutanil; iii. The HIARC determined that a developmental neurotoxicity study is not required; and iv. The exposure assessments will not underestimate the potential dietary (food and drinking water) and residential (non-occupational) exposures for infants and children from the use of myclobutanil.

3.3 Dose Response Assessment

On August 12, 1999, the HIARC reassessed the need for an acute dietary endpoint. The HIARC had previously met on October 21, 1997 (document dated 03-NOV-1997) to evaluate the toxicology database of myclobutanil with special reference to the reproductive, developmental and neurotoxicity data. These data were re-reviewed at that time specifically to address the sensitivity of infants and children from exposure to myclobutanil as required by the FQPA of 1996. In addition, the Committee also re-assessed the doses and endpoints selected for acute dietary, chronic dietary (RfD) as well as occupational and residential exposure risk assessments that had been established. There were previous meetings of the HED RfD Committee on April 28, 1994 (HED Doc. No. 011074, 6/16/94) and of the HED Toxicology Endpoint Selection (TES) Committee (HED Doc. No. 013469, 7/13/94).

Acute dietary endpoints: The acute dietary endpoint for females in the 13 to 50 year age group is based the NOAEL for a developmental toxicity in rabbits of 60 mg/kg/day which manifested as increases in resorptions, decreases in litter size. This endpoint is considered appropriate for females of child bearing age (13-50 years old) since the effects could occur due to a single *in utero* exposure.

There were no appropriate toxicological effects attributable to a single exposure (dose) observed in oral toxicity studies including the maternal effects in the developmental toxicity studies in rats and rabbits. Therefore, a dose and an endpoint were not selected for the general population for this risk assessment.

Chronic dietary endpoint: The chronic dietary endpoint is based on increased incidence of testicular atrophy in a chronic toxicity/carcinogenicity study in rats at the NOAEL of 2.5 mg/kg/day and the LOAEL of 10 mg/kg/day. The Committee noted that the dose of 2.49 mg/kg/day established in the above study is supported by the Parental Systemic Toxicity NOAEL and LOAEL established in the Two-Generation reproduction study in rats. In that study the NOAEL was 2.5 mg/kg/day and the LOAEL was 10 mg/kg/day.

Short-Term (1-7 days) Oral Exposure: The short-term oral exposure endpoint is based on atrophy of the testes and prostate as well as an increase in the number of stillborn pups and a decrease in pup weight gain during lactation in a two-generation reproduction study in rat. The NOAEL was 10 mg/kg/day and the LOAEL was 50 mg/kg/day. Since an oral dose is selected, the dermal absorption factor of 50% should be applied (RAB1 Tox. Committee, 7/27/05, personal communication).

Intermediate-Term (7 days to several mo.) Oral Exposure: The intermediate-term oral exposure endpoint is based on atrophy of the testes and prostate as well as an increase in the number of stillborn pups and a decrease in pup weight gain during lactation in a two-generation reproduction study in rat. The NOAEL was 10 mg/kg/day and the LOAEL was 50 mg/kg/day. Since an oral dose is selected, the dermal absorption factor of 50% should be applied (RAB1 Tox. Committee, 7/27/05, personal communication).

Dermal Absorption: The Committee determined (August 12, 1999) that a dermal absorption factor of 50 % should be used for risk assessment based on a dermal absorption study (MRID 00165252). Although this study is considered unacceptable, the study provides information indicating that absorption would be no greater than 50 %. The dermal absorption factor is required for intermediate and long-term dermal risk assessment since oral doses were selected for these exposure periods. Dermal absorption is not required for short-term dermal exposure risk assessment since a dermal dose from a 21-day dermal toxicity study was selected for this time period.

Short-Term (1-7 days) Dermal Exposure: The short-term dermal exposure endpoint is based on microscopic changes, indicating irritation were observed in the skin, including epidermal necrosis, epidermal thickening, and/or subacute/chronic inflammation of the dermis in a 28-day

dermal toxicity in rat. The NOAEL for systemic effects is greater than 100 mg a.i./kg/day. No systemic toxicity was observed at the highest dose.

Intermediate-Term (7 days to several mo.) Dermal Exposure: The intermediate-term dermal exposure endpoint is based on atrophy of the testes and prostate as well as an increase in the number of stillborn pups and a decrease in pup weight gain during lactation in a two-generation reproduction study in rat. The NOAEL was 10 mg/kg/day and the LOAEL was 50 mg/kg/day. Since an oral dose is selected, the dermal absorption factor of 50% should be applied.

Long-Term (Several Months to Life-Time) Dermal Exposure: The long-term dermal endpoint is based on increased incidence of testicular atrophy in a chronic toxicity/carcinogenicity study in rats at the NOAEL of 2.5 mg/kg/day and the LOAEL of 10 mg/kg/day. The Committee noted that the dose of 2.49 mg/kg/day established in the above study is supported by the Parental Systemic Toxicity NOAEL and LOAEL established in the Two-Generation reproduction study in rats. In that study the NOAEL was 2.5 mg/kg/day and the LOAEL was 10 mg/kg/day. Since an oral dose is selected, the dermal absorption factor of 50% should be applied.

Short-(1-7 days) and Intermediate-Term (7 days to several mo.) Inhalation Exposure: The short- and long-term inhalation endpoint is based on increased incidence of testicular atrophy in a chronic toxicity/carcinogenicity study in rats at the NOAEL of 2.5 mg/kg/day and the LOAEL of 10 mg/kg/day. The Committee noted that the dose of 2.49 mg/kg/day established in the above study is supported by the Parental Systemic Toxicity NOAEL and LOAEL established in the Two-Generation reproduction study in rats. In that study the NOAEL was 2.5 mg/kg/day and the LOAEL was 10 mg/kg/day. The inhalation exposure component (i.e., mg/L) using a 100 % absorption rate (default value) should be converted to an oral equivalent dose (mg/kg/day). This oral equivalent dose should then be compared to the oral NOAEL of 10 mg/kg/day for Short- and Intermediate-Term exposure to calculate the Margins of Exposure (MOE).

Long-Term (Several Months to Life-Time) Inhalation Exposure: The long-term dermal endpoint is based on increased incidence of testicular atrophy in a chronic toxicity/carcinogenicity study in rats at the NOAEL of 2.5 mg/kg/day and the LOAEL of 10 mg/kg/day. The Committee noted that the dose of 2.49 mg/kg/day established in the above study is supported by the Parental Systemic Toxicity NOAEL and LOAEL established in the Two-Generation reproduction study in rats. In that study the NOAEL was 2.5 mg/kg/day and the LOAEL was 10 mg/kg/day. The inhalation exposure component (i.e., mg/L) using a 100 % absorption rate (default value) should be converted to an oral equivalent dose (mg/kg/day). This oral equivalent dose should then be compared to the oral NOAEL of 2.49 mg/kg/day for Long-Term exposures to calculate the Margins of Exposure.

For Occupational/Residential Exposure All durations: A MOE of 100 is adequate to ensure protection from occupational exposures to myclobutanil by dermal and inhalation routes.

Recommendation for Aggregate Exposure Risk Assessments: For acute aggregate exposure risk assessment, combine the high-end exposure values from food+water and compare them to the acute PAD.

For short-term aggregate exposure risk assessment, even though there was no systemic toxicity in a dermal study, by combining dermal with oral and inhalation exposures would provide the most conservative risk assessment approach (RAB1 Tox. Committee, 7/27/05, personal communication).

For intermediate- and chronic-term aggregate exposure risk assessment, oral, dermal and inhalation exposures can be combined since dermal and inhalation exposures are corrected to oral equivalent doses.

Carcinogenic Potential: The HED CPRC classified myclobutanil as Group E - not likely human carcinogen.

The doses and toxicological endpoints selected for various exposure scenarios are summarized below.

TABLE 3. SUMMARY OF TOXICOLOGICAL DOSES AND ENDPOINTS FOR MYCLOBUTANIL FOR USE IN HUMAN HEALTH RISK ASSESSMENT			
EXPOSURE SCENARIO	DOSE USED IN RISK ASSESSMENT, UF	HAZARD AND EXPOSURE BASED SPECIAL FQPA SAFETY FACTOR	STUDY AND TOXICOLOGICAL EFFECTS
Acute Dietary (Females 13-50)	NOEL = 60 mg/kg/day UF = 100 Acute RfD = 0.6 mg/kg/day	FQPA SF = 1X aPAD = acute RfD = 0.6 mg/kg/day	Developmental Toxicity Study - Rats. LOAEL = 200 mg/kg/day based on increased resorptions, decreased litter size
Acute Dietary (General Population)	None	N/A	N/A
Chronic Dietary (All populations)	NOAEL = 2.49 mg/kg/day UF = 100 Chronic RfD = 0.025 mg/kg/day	FQPA SF = 1X cPAD = chronic RfD = 0.025 mg/kg/day	Chronic Toxicity/Oncogenicity Study - Rats LOAEL = 10 mg/kg/day based on decreased testicular weights and increased testicular atrophy
Short-Term (1-30 days) Oral	Oral NOAEL = 10 mg ai/kg/day	Residential MOE = 100 Occupational MOE = 100	2-Generation Reproduction Toxicity - Rat. LOAEL = 50 mg/kg bw/day based on atrophy of the testes and prostate as well as an increase in the number of stillborn pups and a decrease in pup weight gain during lactation.

TABLE 3. SUMMARY OF TOXICOLOGICAL DOSES AND ENDPOINTS FOR MYCLOBUTANIL FOR USE IN HUMAN HEALTH RISK ASSESSMENT

EXPOSURE SCENARIO	DOSE USED IN RISK ASSESSMENT, UF	HAZARD AND EXPOSURE BASED SPECIAL FQPA SAFETY FACTOR	STUDY AND TOXICOLOGICAL EFFECTS
Intermediate-Term (1-6 months) Oral	Oral NOAEL = 10 mg ai/kg/day	Residential MOE = 100 Occupational MOE = 100	2-Generation Reproduction Toxicity - Rat. LOAEL = 50 mg/kg bw/day based on atrophy of the testes and prostate as well as an increase in the number of stillborn pups and a decrease in pup weight gain during lactation.
Short-Term (1-30 days) Dermal	NOAEL = 100 mg ai/kg/day	Residential MOE = 100 Occupational MOE = 100	28-day Dermal Toxicity - Rats. There were no signs of toxicity at the high dose of 100 mg/kg a.i.
Intermediate-Term (1-6 months) Dermal	Oral NOAEL = 10 mg ai/kg/day	Residential MOE = 100 Occupational MOE = 100	2-Generation Reproduction Toxicity - Rat. LOAEL = 50 mg/kg bw/day based on atrophy of the testes and prostate as well as an increase in the number of stillborn pups and a decrease in pup weight gain during lactation.
Long-Term Dermal (> 6 months)	Oral NOAEL = 2.49 mg/kg/day	Residential MOE = 100 Occupational MOE = 100	Chronic Toxicity/Carcinogenicity - Rat LOAEL = 10 mg/kg/day based on decreased testicular weights and increased testicular atrophy.
Short-Term (1-30 Days) Inhalation	Oral NOAEL = 10 mg/kg/day	Residential MOE = 100 Occupational MOE = 100	2-Generation Reproduction Toxicity Study - Rats. LOAEL = 50 mg/kg bw/day based on atrophy of the testes and prostate as well as an increase in the number of stillborn pups and a decrease in pup weight gain during lactation.
Intermediate-Term (1-6 months) Inhalation	Oral NOAEL = 10 mg/kg/day	Residential MOE = 100 Occupational MOE = 100	2-Generation Reproduction Toxicity Study - Rats. LOAEL = 50 mg/kg bw/day based on atrophy of the testes and prostate as well as an increase in the number of stillborn pups and a decrease in pup weight gain during lactation.

TABLE 3. SUMMARY OF TOXICOLOGICAL DOSES AND ENDPOINTS FOR MYCLOBUTANIL FOR USE IN HUMAN HEALTH RISK ASSESSMENT			
EXPOSURE SCENARIO	DOSE USED IN RISK ASSESSMENT, UF	HAZARD AND EXPOSURE BASED SPECIAL FQPA SAFETY FACTOR	STUDY AND TOXICOLOGICAL EFFECTS
Long-Term Inhalation (> 6 months)	Oral NOAEL = 2.49 mg/kg/day	Residential MOE = 100 Occupational MOE = 100	Chronic Toxicity/Carcinogenicity - Rat LOAEL = 10 mg/kg/day based on decreased testicular weights and increased testicular atrophy.
Cancer	Group E- likely not a human carcinogen		

3.4 Endocrine Disruption

EPA is required under the Federal Food Drug and Cosmetic Act (FFDCA), as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there was scientific basis for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA has authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

When the appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, myclobutanil may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

4.0 EXPOSURE ASSESSMENT

4.1 Summary of Registered Uses

Tolerances are established for combined residues of the fungicide myclobutanil [α -butyl- α -(4-chlorophenyl)-1*H*-1,2,4-triazole-1-propanenitrile] and its alcohol metabolite [α -(3-hydroxybutyl)- α -(4-chlorophenyl)-1*H*-1,2,4-triazole-1-propanenitrile] (free and bound) [40 CFR §180.443(a)], ranging from 0.02 ppm on cotton seed and eggs to 25 ppm on grape raisin

waste. Time-limited tolerances [40 CFR §180.443(b)] and tolerances for inadvertent residues [40 CFR §180.443(d)] have also been established.

4.2 Proposed Uses

Proposed application parameters in the Section 18 request call for up to 2 applications of myclobutanil at an application rate of 2.0 oz (0.125 lb) a.i./A, equivalent to approximately 56 g a.i./A. The Section 18 requested a PHI of 28 days. The Section 18 for legume vegetables proposed up to 2 applications for a total of 0.50 lb a.i./A/season with 5-11 day retreatment intervals and 0-day PHI

TABLE 4. FOOD/FEED USE PATTERNS FOR MYCLOBUTANIL.						
SITE APPLICATION TYPE APPLICATION EQUIPMENT	FORM. [EPA REG. NO.]	MAX. SINGLE APP. RATE (LB AI/A)	MAX. NUMBER OF APP.. PER SEASON	MAX. SEASONAL RATE (LB AI/A)	PHI (DAYS)	USE DIRECTIONS AND LIMITATIONS
Soybeans						
Ground foliar	Laredo EC [62719-412] Laredo EW [62719-493]	0.125	2	0.250	28	The feeding of treated soybean forage and hay to livestock is prohibited.
Legume Vegetables (Except Soybeans)						
Ground foliar	Nova 40W [62719-00411] Rally 40W [62719-00411]	0.25	2	0.50	0	

4.3 Water Exposure/Risk Pathway

There are no health advisory levels or Maximum Contaminant Levels established for residues of myclobutanil in drinking water. The Agency used SCI-GROW to calculate myclobutanil EECs in ground water and FIRST to calculate EECs in surface water. Model assumptions followed the use patterns for hops: 15 applications per year, 0.65 lb a.i./application, and 14 day PHI (DP Barcode D289700 and D290167, T. Nguyen, 6/9/03). These assumptions are much higher than the proposed patterns in the Section 18. Based on the FIRST model, the EECs of myclobutanil for acute exposures are 333 ppb and 86 ppb for chronic exposures. The EEC for both acute and chronic exposures is estimated as 3.2 ppb for surface water using the SCI-GROW model.

TABLE 5. ESTIMATED TIER 1 CONCENTRATIONS OF MYCLOBUTANIL IN DRINKING WATER.		
Chemical	Surface Water (ug/L)	Groundwater (ug/L)

	Acute	Chronic	Acute and Chronic
Myclobutanil	333	86	3.2

4.4 Dietary Exposure/Risk Pathway

4.4.1 Residue Profile

The nature of the residue in plants is adequately understood. The nature of the residue in plants was determined by HED in previous reviews of myclobutanil metabolism in wheat (PP#4G3149, Memo, R. Loranger, 1/9/85), and grapes and apples (PP#7G3479, Memo, R. Loranger, 6/16/87). The residues of concern are myclobutanil [α -butyl- α -(4-chlorophenyl)-1H-1,2,4-triazole-1-propanenitrile] and its metabolite [α -(3-hydroxybutyl)- α -(4-chlorophenyl)-1H-1,2,4-triazole-1-propanenitrile] (free and bound), as specified in 40 CFR 180.443(a).

The nature of the residue in livestock is adequately understood. Myclobutanil metabolism in meat, milk, poultry, and eggs has been reviewed in conjunction with PP#7F3476 (M. Nelson, 2/8/88) and summarized in conjunction with the temporary tolerance petition for almond nuts and hulls (PP#9G3786, J. Smith, 12/6/89). The residues of concern in livestock commodities except milk are myclobutanil [α -butyl- α -(4-chlorophenyl)-1H-1,2,4-triazole-1-propanenitrile] and its metabolite α -(3-hydroxybutyl)- α -(4-chlorophenyl)-1H-1,2,4-triazole-1-propanenitrile (free). The residues of concern in milk are myclobutanil [α -butyl- α -(4-chlorophenyl)-1H-1,2,4-triazole-1-propanenitrile] and its metabolites, α -(3-hydroxybutyl)- α -(4-chlorophenyl)-1H-1,2,4-triazole-1-propanenitrile (free and bound) and α -(4-chlorophenyl)- α -(3,4-dihydroxybutyl)-1H-1,2,4-triazole-1-propanenitrile.

An adequate enforcement method for plant commodities, Rohm and Haas Method 34S-88-10, is available to enforce the proposed tolerances. Quantitation is by GLC using a nitrogen/phosphorus detector for myclobutanil and an electron capture detector (Ni^{63}) for the alcohol metabolite (PP#7F3476, MRID# 40803302, M. Nelson, 4/14/88). Enforcement methods for the established tolerances on livestock commodities are Methods 34S-88-22 (MRID #40825301), 34S-88-15 (MRID #40645801), 31S-87-02 (MRID #40481301), and 34S-88-21 (MRID #40803301). These methods have been submitted for publication in PAM II (PP#7F3476, M. Nelson, 7/18/89).

Storage stability studies for myclobutanil on apples and grapes have been reviewed by HED (PP#7F3476, Accession#s 266109 & 266115, M. Nelson, 2/8/88). In another submission, apples and grapes were reanalyzed for myclobutanil and its metabolite after frozen storage (PP#7F3476, M. Nelson, 4/26/88). Grapes and apples treated with myclobutanil, harvested, analyzed, and stored over 3 years and reanalyzed for both myclobutanil and its metabolite showed no change in the levels or composition of the residues demonstrating the long-term stability of myclobutanil and its metabolite in samples for at least 3 years under frozen conditions. Additional storage stability studies demonstrate that myclobutanil and its alcohol metabolite are stable under frozen conditions for the following time periods: 288 days in/on asparagus (DP Barcode: D238442,

MRID#s 44318901 and -02, G. Kramer, 12/11/98;); 657 days (22 months) in/on snap beans (DP Barcode: D238454, MRID# 44338201, N. Dodd, 4/24/98); 296 days in/on mint (DP Barcode: D238448, MRID# 44349601, J. Rowell, 8/3/99); and 36 months in/on tomatoes (DP Barcode: D251632, MRID# 44679804, J. Rowell, 9/1 3/99).

The registrant has supplied information that the existing time-limited tolerances for soybeans are inadequate as a result of preliminary data from ongoing domestic field trials. The summary of the preliminary data indicates that a tolerance of 0.05 ppm for the residues of myclobutanil on soybeans would be appropriate rather than the existing 0.03 ppm.

No magnitude of the residue data was submitted in support of the Section 18 request for legume vegetables (except soybeans). The results of magnitude of the residue study on snap beans have been submitted by IR-4 (MRID# 44338201). These data were reviewed by HED and determined to be inadequate due to deficiencies pertain to the Section B/label, residue data, and rotational crop data (N. Dodd, 4/24/98; D238454). A total of 7 trials reflecting the maximum proposed use rate per application and per season were conducted between the 1989 and 1992 growing seasons in the states of FL(1), GA(1), MI(1), NY(1), OR(1), TN(1), and WI(1), representing Regions 1 (1 trial), 2 (2 trials), 3 (1 trial), 5 (2 trials), and 11 (1 trial). The available data indicate that the combined residues of myclobutanil and its metabolite RH-9090 did not exceed the proposed tolerance level of 1.0 ppm in/on snap beans harvested 0 days following the last of multiple foliar applications, with 5-11 day retreatment intervals, of the 40% WP formulation at 0.50 lb ai/A/season (1x the maximum proposed seasonal rate). A time-limited tolerance of 1.0 ppm is appropriate for residues of myclobutanil and its alcohol metabolite in/on vegetable, legume (except soybean), Crop Group 6 and vegetable, foliage of legume (except soybean), Crop Group 7.

Also included in this analysis are the tolerances for inadvertent residues listed below in support of an upcoming risk assessment (PP# 7E4861, DP Barcode: 308904. MRID#s 461711901, 461711902, and 46034003, J. Tyler, in process).

TABLE 6. ADDITIONAL MYCLOBUTANIL AND ROTATIONAL CROP TOLERANCES	
Commodity	ppm
Vegetable, Root and Tuber, Group	0.10
Vegetable, Leaves of Root and Tuber, Group	0.20
Vegetable, Leafy, Except Brassica, Group	1.0
Vegetable, Brassica Leafy, Group	1.0
Vegetable, Fruiting, Group	1.0
Grains, Cereal, Group	0.03

Since the tolerances on livestock commodities were established based on almond hulls at 2 ppm, wet grape pomace at 10 ppm, and raisin waste at 25 ppm, the addition of soybeans at 0.05 ppm or 1.0 ppm on vegetable, legume (except soybean), Crop Group 6 and vegetable, foliage of legume (except soybean), Crop Group 7 would not materially increase the dietary burden to livestock. Therefore, no increase in the tolerances on livestock commodities is required as a result of the increase in the soybean tolerance or establishment of time-limited tolerances of 1.0

ppm on vegetable, legume (except soybean), Crop Group 6 and vegetable, foliage of legume (except soybean), Crop Group 7.

Current status sheets indicate that no Codex, Canadian, or Mexican maximum residue levels (MRLs) have been established for residues of myclobutanil on soybeans or legume vegetables (except soybeans). Therefore, there are no international harmonization issues associated with this action.

4.4.2 Acute Dietary

Acute Dietary Exposure and Risk.

Females (13-50) aPAD = acute RfD = 0.6 mg/kg bwt/day.

The acute analysis is a conservative Tier 1 assessment based on tolerance-level residues and the assumption of 100% crop treated for established and proposed myclobutanil tolerances. Tolerances are established for myclobutanil in 40 CFR §180.443. DEEM default processing factors from DEEM (Version 7.76) were used for all processed commodities that do not have individual tolerances. The highest estimate for acute water exposure, 333 ppb, was used in the analysis.

As this is a Tier 1 assessment, dietary exposure and risk at the 95th percentile of exposure are reported. For females 13-49 yrs old, the only population subgroup for which there is a myclobutanil acute endpoint has exposure and risk estimates which are below HED's level of concern (i.e., the percentages of the aPADs are below 100%). The exposure estimate for females 13-49 yrs old is 4% aPAD.

TABLE 7. RESULTS OF ACUTE DIETARY EXPOSURE ANALYSIS USING DEEM FCID							
Population Subgroup	aPAD (mg/kg/day)	95 th Percentile		99 th Percentile		99.9 th Percentile	
		Exposure (mg/kg/day)	% aPAD	Exposure (mg/kg/day)	% aPAD	Exposure (mg/kg/day)	% aPAD
Females 13-49 years old	0.6	0.026567	4	0.037883	6	0.060209	10

4.4.3 Chronic Dietary

Chronic Dietary Exposure and Risk cPAD = chronic RfD = 0.025 mg/kg bwt/day.

The chronic analysis is based on partially refined Tier 3 assumptions in that it incorporates estimates of average percent crop treated (%CT) for some crops, as well as Pesticide Data Program (PDP) monitoring data from apple juice, bananas (not plantains) and milk (as part of the risk assessment in support of a Section 18 request (04MN006, DP Barcode: D296308, J. Tomerlin, 3/22/04). The following average %CT information was used: apples, 40%; apricots, 15%; cherries, 40%; grapes, 45%; nectarines, 20%; peaches, 10%; plums, 15%; and cotton, 1%. This information was obtained from the Biological Economic and Analysis Division (BEAD) (Memo, F. Hernandez, 9/7/99). 100% CT was assumed for all other commodities. DEEM

default processing factors from DEEM (Version 7.76) were used for all processed commodities that do not have individual tolerances. The highest estimate for chronic water exposure, 86 ppb, was used in the analysis.

The general U.S. population and all population subgroups have exposure and risk estimates which are below HED's level of concern (i.e., the percentages of the cPADs are all below 100%). The exposure estimate for the U.S. population is 20% cPAD and for the most highly exposed subgroup, all infants <1 yrs old, is 41% cPAD.

TABLE 8. RESULTS OF CHRONIC DIETARY EXPOSURE ANALYSIS USING DEEM FCID					
Population Subgroup	aPAD (mg/kg/day)	Chronic		Cancer	
		Dietary Exposure (mg/kg/day)	%cPAD	Dietary Exposure (mg/kg/day)	Risk
General U.S. Population	0.025	0.005234	21	NA	NA
All Infants (< 1 year old)	0.025	0.010238	41		
Children 1-2 years old	0.025	0.011230	45		
Children 3-5 years old	0.025	0.009508	38		
Children 6-12 years old	0.025	0.006219	25		
Youth 13-19 years old	0.025	0.004069	16		
Adults 20-49 years old	0.025	0.004509	18		
Adults 50+ years old	0.025	0.004755	19		
Females 13-50 years old	0.025	0.004437	18		

4.4.4 Cancer Dietary

The HIARC classified myclobutanil as a "Group E - not likely human carcinogen" and, therefore, quantification of human cancer risk is not required.

4.5 Residential Exposure/Risk Pathway

Myclobutanil is present in numerous end-use products, including those registered for use on turf, roses, flowers, shrubs and trees. Soluble concentrate may be applied with hose-end or trigger bottle sprayers. Small scale lawn application has the greatest potential for homeowner exposures. Short and intermediate-term exposures are expected for residential handlers. The

HIARC has determined that a 50% dermal absorption factor should be applied for intermediate-term assessments. A dermal absorption factor is not required for short-term assessments because the NOAEL used is based upon a 28-day dermal study.

The most recent residential risk assessment was conducted for the Section 18 on sugar beets and residential usage has not changed since that time (ID#: 00ID0034, DP Barcode: D268379, J. Rowell, 11/9/00). Therefore, the exposure values summarized in that assessment are valid for the current assessment for the proposed Section 18 on soybean. The residential MOEs are summarized in Tables 9 to 11.

TABLE 9. BASELINE SHORT-TERM MOES FOR HOMEOWNER USE OF MYCLOBUTANIL						
MIX/LOAD/ APPLY EXPOSURE SCENARIO	TOTAL DAILY DOSE (mg/kg/day)		SHORT-TERM MOE		COMBINED SHORT-TERM MOE TURF + ORN. TREATMENT	
	DERMAL	INHALATION	DERMAL	INHALATION	DERMAL	INHALATION
Garden hose application to turfgrass	0.13	0.000044	770	230000	750	230000
Trigger sprayer application to ornamentals	0.0036	0.0000011	28000	9100000		
Dermal NOAEL: 100 mg/kg/day Inhalation NOAEL: 10 mg/kg/day						

TABLE 10. RESIDENTIAL POST-APPLICATION MOES FOR MYCLOBUTANIL						
SCENARIO	DAILY DOSE (mg/kg/day)		SHORT- TERM MOE	INTERM.- TERM MOE	COMBINED MOE	
	SHORT	INTERM			SHORT	INTERM
Adult dermal - turf	0.073	0.022 ¹	1400	450	1100	N/A
Adult dermal - ornamentals	0.017	N/A	5900	N/A		
Toddler - hand-to-mouth	0.07	0.033	140	300	120	140
Toddler dermal - turf	0.12	0.036	830	280		
Toddler-oral-soil ingestion	0.00031	N/A	32000	N/A	N/A	N/A

TABLE 10. RESIDENTIAL POST-APPLICATION MOES FOR MYCLOBUTANIL

Short-Term dermal 100 mg/kg/day Short-term oral NOAEL 10 mg/kg/day
 Intermediate-Term dermal 10 mg/kg/day Intermediate-term oral NOAEL 10 mg/kg/day
¹ Incorporates a 50% dermal absorption factor

TABLE 11. COMBINED RESIDENTIAL HANDLER AND POST-APPLICATION DERMAL EXPOSURES

SCENARIO	SHORT-TERM MOE	COMBINED SHORT-TERM MOE
Handler applying to turf and ornamentals	750	450
Adult post-application exposure to turf and ornamentals	1100	

Since MOEs less than 100 are of concern, there are no residential risk concerns for myclobutanil.

5.0 AGGREGATE RISK ASSESSMENT AND RISK CHARACTERIZATION

5.1 Acute Risk

The aggregate acute dietary risk estimates include exposure to residues of myclobutanil in food and water, and does not include dermal, inhalation or incidental oral exposure. Since the dietary exposure assessment already includes the highest acute exposure from the drinking water modeling data, no further calculations are necessary. The population subgroup of interest, females 13-49 yrs old, has exposure and risk estimates which are below HED's level of concern (i.e., the percentages of the aPADs are below 100%). The food and water exposure estimates for females 13-49 yrs old is 4 % aPAD. Therefore, the acute aggregate risk estimates associated with the proposed use of myclobutanil do not exceed HED's level of concern.

5.2 Short- and Intermediate-Term Risk

Aggregate Short-Term Risk

For short-term aggregate exposure risk assessment, even though there was no systemic toxicity in a dermal study, by combining dermal with oral and inhalation exposures would provide the most conservative risk assessment approach. Since all the acceptable short-term MOEs are 100 but the NOAELs vary (short-term dermal NOAEL is 100 mg/kg/day, all others are 10 mg/kg/day), the reciprocal equation approach will be used to calculate aggregate short-term risk estimates. The aggregate short-term exposure estimates are below HED's level of concern (MOEs < 100).

TABLE 12. SHORT-TERM AGGREGATE RISK

Population	Target MOE	Short-Term Scenario					
		Food + Water			Dermal MOE ⁴	Oral MOE ⁴	Aggregate MOE ⁵
		NOAEL ¹ (mg/kg/day)	Average Food + Water Exposure ² (mg/kg/day)	MOE ³			
Children 1-2 yrs old	100	10	0.011230	890	830	140	110
US Population	100	10	0.005234	1900	1400	NA	800

¹ Short-term Oral NOAEL
² Chronic Food from Table 8
³ MOE = NOAEL/Exposure
⁴ Residential MOE from Table 10
⁵ Aggregate MOE = $[1 \div ((1/\text{MOE}_{\text{Food+Water}}) + (1/\text{MOE}_{\text{Dermal}}) + (1/\text{MOE}_{\text{Oral}}))]$

Aggregate Intermediate-Term Risk

For myclobutanil intermediate-term aggregate exposure risk assessment, oral, dermal and inhalation exposures can be combined since dermal and inhalation exposures are corrected to oral equivalent doses. The aggregate intermediate-term exposure estimates for myclobutanil do not include inhalation exposure, as there is no associated scenario. The aggregate intermediate-term exposure estimates are below HED's level of concern (MOEs < 100).

TABLE 13. INTERMEDIATE-TERM AGGREGATE RISK

Population	Intermediate-Term Scenario						
	NOAEL (mg/kg/day)	Max Allowable Exposure ¹ (mg/kg/day)	Average Food + Water Exposure (mg/kg/day)	Dermal Exposure (mg/kg/day)	Oral Exposure (mg/kg/day)	Residential Exposure ² (mg/kg/day)	Aggregate MOE ³
Children 1-2 yrs old	10	0.1	0.011230	0.018	0.0013	0.0193	330
US Population	10	0.1	0.005234	0.011	NA	0.011	620

¹ Maximum Exposure (mg/kg/day) = NOAEL/Target MOE of 100
² Residential Exposure = The combined dermal and incidental oral ingestion for infants and dermal only for adults. Residential Exposure from Table 10.
³ Aggregate MOE = $[\text{NOAEL} \div (\text{Avg Food \& Water Exposure} + \text{Residential Exposure})]$

5.3 Chronic Risk

For myclobutanil chronic aggregate exposure risk assessment, oral, dermal and inhalation exposures can be combined since dermal and inhalation exposures are corrected to oral equivalent doses. However, there are no chronic residential dermal or inhalation scenarios, therefore the assessment included food and water only. Since the dietary exposure assessment already includes the highest chronic exposure from the drinking water modeling data, no further calculations are necessary. The general U.S. population and all population subgroups have exposure and risk estimates which are below HED's level of concern (i.e., the percentages of the cPADs are all below 100%). The exposure to the U.S. population was 21% cPAD and the most highly exposed subgroup, children 1-2 yrs old, at 45% cPAD. Therefore, the aggregate chronic risk associated with the proposed use of myclobutanil does not exceed the Agency's level of concern for the general U.S. population or any population subgroup.

5.4 Cancer Risk

The HIARC classified myclobutanil as a "Group E - not likely human carcinogen" and, therefore, quantification of human cancer risk is not required.

6.0 CUMULATIVE RISK

FQPA (1996) stipulates that when determining the safety of a pesticide chemical, EPA shall base its assessment of the risk posed by the chemical on, among other things, available information concerning the cumulative effects to human health that may result from dietary, residential, or other non-occupational exposure to other substances that have a common mechanism of toxicity. The reason for consideration of other substances is due to the possibility that low-level exposures to multiple chemical substances that cause a common toxic effect by a common mechanism could lead to the same adverse health effect as would a higher level of exposure to any of the other substances individually. A person exposed to a pesticide at a level that is considered safe may in fact experience harm if that person is also exposed to other substances that cause a common toxic effect by a mechanism common with that of the subject pesticide, even if the individual exposure levels to the other substances are also considered safe.

HED did not perform a cumulative risk assessment as part of this tolerance action for myclobutanil because HED has not yet initiated a review to determine if there are any other chemical substances that have a mechanism of toxicity common with that of myclobutanil. For purposes of this tolerance action, EPA has assumed that myclobutanil does not have a common mechanism of toxicity with other substances.

On this basis, the Registrant must submit, upon EPA's request and according to a schedule determined by the Agency, such information as the Agency directs to be submitted in order to evaluate issues related to whether myclobutanil shares a common mechanism of toxicity with any other substance and, if so, whether any tolerances for myclobutanil need to be modified or revoked. If HED identifies other substances that share a common mechanism of toxicity with myclobutanil, HED will perform aggregate exposure assessments on each chemical and will begin to conduct a cumulative risk assessment.

HED has recently developed a framework that it proposes to use for conducting cumulative risk assessments on substances that have a common mechanism of toxicity. This guidance was issued for public comment on January 16, 2002 (67 FR 2210-2214) and is available from the OPP Website at: http://www.epa.gov/pesticides/trac/science/cumulative_guidance.pdf. In the guidance, it is stated that a cumulative risk assessment of substances that cause a common toxic effect by a common mechanism will not be conducted until an aggregate exposure assessment of each substance has been completed.

Before undertaking a cumulative risk assessment, HED will follow procedures for identifying chemicals that have a common mechanism of toxicity as set forth in the *"Guidance for Identifying Pesticide Chemicals and Other Substances that Have a Common Mechanism of Toxicity"* (64 FR 5795-5796, February 5, 1999).

7.0 OCCUPATIONAL EXPOSURE AND RISK

Although the existing risk assessment and inadvertent residues tolerances on soybeans is being used to support the Section 18 request of the use of myclobutanil on soybeans and legumes, it was necessary to conduct an assessment of worker risk using the soybean and legume use patterns. For myclobutanil, toxicity endpoints were taken from HIARC 9/2/99. The dermal toxicological endpoint (NOAEL 100 mg a.i./kg bw/day) was taken from a 28-day dermal toxicity study in the rat. Therefore, there was no correction for dermal absorption. The inhalation toxicological endpoint (NOAEL 10 mg a.i./kg bw/day) was taken from a 2-generation reproduction toxicity study in the rat where the effects seen were atrophy of the testes and prostate as well as an increase in the number of stillborn pups and a decrease in pup weight gain during lactation. The ADD for dermal exposure for myclobutanil is calculated as

$$\text{ADD} = \text{Unit Exposure} * \text{Application Rate} * \text{Units Treated} \div 70 \text{ kg bw}$$

Since the inhalation endpoint was taken from a developmental study showing fetal effects (it was a repro study), 60 kg is used to calculate inhalation exposure. Bill-I am not sure we should be using 60 kg...I need to confirm. Waiting to hear from Karen. My calculations are using 70 kg for inhalation risk. A summary of the worker risk calculations is provided in Table 14.

TABLE 14. SUMMARY OF EXPOSURES AND RISKS TO OCCUPATIONAL PESTICIDE HANDLERS FOR MYCLOBUTANIL TO CONTROL SOYBEAN RUST IN LEGUMES AND SOYBEANS.					
Unit Exposure ¹ mg/lb ai handled	Application Rate ² lb ai/Acre	Units Treated ³ Acres/Day	Average Daily Dose ⁴ mg a.i./kg bw/day	NOAEL ⁵ mg a.i./kg bw/day	MOE ⁶
Mixer/Loader - Liquid - Open Loading					
Dermal: SLNG 2.9 HC SLWG 0.023 HC Inhal 0.0012HC	0.25	1200	Dermal SLNG 12 SLWG 0.10 Inhalation 0.005	Dermal 100 from 28 day dermal Inhalation 10	Dermal SLNG 8 SLWG 1000 Inhalation 2000
Applicator - Ground-boom - Open Cab					
Dermal: SLNG 0.014 HC SLWG 0.014 MC Inhal 0.00074HC	0.25	200	Dermal SLNG 0.01 SLWG 0.01 Inhalation 0.00053	Dermal 100 from 28 day dermal Inhalation 10	Dermal SLNG 10,000 SLWG 10,000 Inhalation 19,000
Applicator - Aerial - Fixed Wing					
Dermal: SLNG 0.0050 MC Inhal 0.000068 MC	0.25	1200	Dermal 0.021 Inhalation 0.00029	Dermal 100 from 28 day dermal Inhalation 10	Dermal 4,700 Inhalation 34,000
<p>1. Unit Exposure = mg a.i./lb a.i. handled from PHED SURROGATE EXPOSURE GUIDE - Estimates of Worker Exposure from the Pesticide Handler Exposure Database Version 1.1, August 1998. Dermal: SLNG = a Single Layer of work clothing (i.e., long pants, long-sleeved shirt, shoes plus socks) and No protective gloves. SLWG = a single layer of work clothing and the use of protective gloves (i.e., with gloves). Inhal = Inhalation exposure.</p> <p>2. Application Rate taken from Section 18 Request, Corresp. J. Sierk Minnesota Dept. Agricult. to D. Rosenblatt, 30 January 2004.</p> <p>3. Units Treated taken from Science Advisory Council for Exposure, Standard Operating Procedure 9.1, Standard Values for Daily Acres Treated in Agriculture, Rev. 25 SEP 2001.</p> <p>4. Average Daily Dose (ADD) is derived by: Unit Exposure * Application Rate * Units Treated ÷ Body Weight.</p> <p>NOTE a) Dermal absorption is not corrected if the toxicological endpoints were identified from a dermal toxicity study Inhalation absorption is assumed to be 100 %.</p> <p>NOTE b) Body weight is assumed to be 70 kg</p> <p>5. No Observed Adverse Effect Level (NOAEL) (mg a.i./kg bw/day) is taken from the HIARC report.</p> <p>6. Margin Of Exposure (MOE) = NOAEL (mg a.i./kg bw/day) ÷ ADD (mg a.i./kg bw/day).</p>					

There is a potential for agricultural workers to have post-application exposure to pesticides during the course of typical agricultural activities. Health Effects Division in conjunction with the Agricultural Re-entry Task Force (ARTF) has identified a number of post-application agricultural activities that may occur. HED has also identified Transfer Coefficients (TC)

(expressed as cm²/hr) relative to the various activities.

The transfer coefficients used in this assessment are from an interim transfer coefficient SOP developed by HED's Science Advisory Council for Exposure (ExpoSAC) using proprietary data from the Agricultural Re-Entry Task Force (ARTF) database (SOP # 3.1). It is the intention of the ExpoSAC that this SOP will be periodically updated to incorporate additional information about agricultural practices in crops and new data on transfer coefficients. Much of this information will originate from exposure studies currently being conducted by the ARTF, from further analysis of studies already submitted to the Agency, and from studies in the published scientific literature.

For the proposed use, the activity with the highest TC is scouting the crop in full foliage stages of crop development with a TC of 1,500 cm²/hr.

Lacking compound specific data, the Agency assumes 20 % of the application rate is available as foliar dislodgeable residue on day zero after application. This is adapted from the ExpoSAC SOP No. 003 (5/7/98 - Revised 8/7/00). The following convention may be used to estimate post-application exposure.

Surrogate Dislodgeable Foliar Residue

DFR =

$$\text{application rate} * 20\% \text{ available as dislodgeable residue} * (1-D)^t * 4.54 \times 10^8 \text{ ug/lb} * 2.47 \times 10^{-8} \text{ A/cm}^2$$

and the Average Daily Dose (ADD) =

$$\text{DFR ug/cm}^2 * \text{TC cm}^2/\text{hr} * \text{hr/day} * 0.001 \text{ mg/ug} * 1/70 \text{ kg bw.}$$

For myclobutanil, the calculations are:

$$\begin{aligned} \text{DFR} &= 0.25 \text{ lb a.i./A} * .20 * (1-0)^0 * 4.54 \times 10^8 \text{ ug/lb} * 2.47 \times 10^{-8} \text{ A/cm}^2 \\ &= 0.56 \text{ ug/cm}^2 \end{aligned}$$

$$\begin{aligned} \text{ADD} &= 0.56 \text{ ug/cm}^2 * 1,500 \text{ cm}^2/\text{hr} * 8 \text{ hr/day} * 0.001 \text{ mg/ug} * 1/70 \text{ kg bw} \\ &= 0.096 \text{ mg/kg bw/day} \end{aligned}$$

$$\begin{aligned} \text{Since } \text{MOE} &= \text{NOAEL} \div \text{ADD then } 100 \text{ mg/kg bw/day} \div 0.096 \text{ mg/kg bw/day} \\ &= 1000. \end{aligned}$$

8.0 DATA NEEDS

8.1 Toxicology

None

8.2 Residue Chemistry

None

8.3 ORE

None

- References:
1. HED HIARC Report, Doc. NO. 013740, 9/2/99.
 2. EFED Drinking Water Exposure Assessment, DP Barcode D289700 and D290167, T. Nguyen, 6/9/03
 3. 04MN06 and 04SD03, DP Barcode: D296308, J. Tomerlin, 3/22/04
 4. 04MN06, DP Barcode: D318346, W. Cutchin, in progress.

INTERNATIONAL RESIDUE LIMIT STATUS			
Chemical Name: Myclobutanil	Common Name:	X Proposed tolerance <input type="checkbox"/> Reevaluated tolerance <input type="checkbox"/> Other	Date: 7/1/05
Codex Status (Maximum Residue Limits)		U. S. Tolerances	
<input type="checkbox"/> No Codex proposal step 6 or above <input checked="" type="checkbox"/> No Codex proposal step 6 or above for the crops requested		Petition Number: 04MN006 DP Barcode: D318347 Other Identifier:	
Residue definition (step 8/CXL): myclobutanil		Reviewer/Branch: W. Cutchin/ARIA Residue definition: myclobutanil, (α -butyl- α -(4-chlorophenyl)-1H-1,2,4-triazole-1-propanenitrile) and its metabolite, α -(3-hydroxybutyl)- α -(4-chlorophenyl)-1H-1,2,4-triazole-1-propanenitrile (free and bound)	
Crop (s)	MRL (mg/kg)	Crop(s)	Tolerance (ppm)
		Soybeans	0.05
		Legume Veg. (except Soybeans)	1.0
Limits for Canada		Limits for Mexico	
<input type="checkbox"/> No Limits <input checked="" type="checkbox"/> No Limits for the crops requested (Also, not on any label)		<input type="checkbox"/> No Limits <input checked="" type="checkbox"/> No Limits for the crops requested	
Residue definition (plant products): α -butyl- α -(4-chlorophenyl)-1H-1,2,4-triazole-1-propanenitrile, including the metabolites α -(3-hydroxybutyl)- α -(4-chlorophenyl)-1H-1,2,4-triazole-1-propanenitrile and α -(butyl-3-one)- α -(4-chlorophenyl)-1H-1,2,4-triazole-1-propanenitrile.		Residue definition: myclobutanil	
Crop(s)	MRL (mg/kg)	Crop(s)	MRL (mg/kg)
Notes/Special Instructions: S. Funk, 07/12/05.			



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R112339

Chemical:	Myclobutanil
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HED File Code	14000 Risk Reviews
Memo Date:	08/09/2005
File ID:	DPD317318; DPD317319; DPD318347
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